REMARKS

Status of the Claims

Claims 11 and 13-22 are currently pending in the present application. Claims 1-10, 12, and 23 have been canceled. Claims 11, 13-15, 17, and 18 have been amended to clarify the claimed invention. Claims 19-22 are withdrawn from consideration as being directed to a non-elected invention. Claims 11 and 13-18 are currently examined.

Amendments to the Claims

The amendments to claims 11, 13-15, 17, and 18 do not introduce prohibited new matter.

Support for the amendments to claims 11 and 17 can be found in original claim 2.

Support for the amendment to claim 13 can be found in original claim 13.

Support for the amendment to claim 14 can be found in original claim 14.

Support for the amendments to claims 15 and 18 can be found in original claim 6.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 11 and 13-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action alleges that claims 11 and 17 are vague and indefinite for reciting "wherein the size of the genome of the bacterial strain is equal to or less than 3.2 Mb." Applicants respectfully submit that the claims are not indefinite because the claimed invention is directed to using Gram positive bacteria of a *Streptococcaceae* strain having a genome of less than or equal to 3.2 Mb to produce a desired protein. The claims also include other limitations such as "a *Streptococcaceae* strain" and "does not express a functional HtrA protease." The recited limitations clearly describe the invention.

The Office Action alleges that claims 11 and 17 are vague and indefinite for reciting "culturing a Gram positive bacterial strain that expresses said protein." Applicants respectfully submit that claim 17 does not include the recited limitation and that the claim 11 is not indefinite because the claimed invention encompasses expressing both heterologous and homologous

proteins. Thus, the limitation clearly describes the invention. Also, the claim 11 is a method of using a Gram positive bacteria of a *Streptococcaceae* family, wherein the bacteria strain does not express a functional HtrA protease. Gram positive bacteria of the *Streptococcaceae* family that express a functional HtrA protease are not encompassed by claim 11. However, Gram positive bacteria of the *Streptococcaceae* family, whether naturally occurring or not, that do not express a functional HtrA protease are encompassed by claim 11. Dependent claim 16 is specifically drawn to the embodiments wherein transformed bacteria express a protein of interest.

The Office Action alleges that claims 15 and 18 are indefinite because it is not clear whether "does not express a functional PrtP protease" is in addition to "does not express a functional HtrA protease." Claims 15 and 18 have been amended to insert the word "also" to clarify that both the HtrA protease and the PrtP protease expression are lacking.

Applicants respectfully request withdrawal of the rejection of the claims as being indefinite.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 11 and 13-18 are rejected under 35 U.S.C. § 112, first paragraph, as being enabling only for a method of producing a protein of interest comprising transforming a mutant *L. lactis* bacterium . . . ."

Claim 11 as it now stands is directed to a method of producing a protein of interest comprising culturing a Gram positive bacterial strain of the *Streptococcaceae* family. Applicants respectfully submit that bacteria of the *Streptococcaceae* family include bacteria of the *Lactococcus* genus and *Streptococcus* genus. *Lactococcus lactis* is a species of the *Lactococcus* genus.

As shown in Annexes 5-7, submitted with the response of November 10, 2003, all bacteria of the *Streptococcaceae* family that have been sequenced have a genome of less than 3.2 Mb encoding a single HtrA/degP protein. In contrast, the Gram negative bacteria, such as *Ecoli*, or other Gram positive bacteria, such as *Bacillus subtilis*, have several housekeeping proteases with functions similar to those of HtrA/Deg P. Further, the HtrA proteases of streptococci and the HtrA protease of *Lactococcus lactis* are highly homologous proteins. Accordingly, one would reasonably expect that the inactivation of the HtrA protease in *Lactococcus lactis* would have the same effect as inactivation of the HtrA protease of *Streptococcus*.

Since the claims are directed to culturing a Gram positive bacterial strain of the *Streptococcaceae* family and since the HtrA protease of the *Streptococcaceae* family are highly homologous, the specification provides sufficient guidance to enable the skilled artisan to produce a desired protein comprising culturing a Gram positive bacterial strain of the *Streptococcaceae* family wherein the genome of the bacterial strain is equal to or less than 3.2 Mb and wherein the bacterial strain does not express a functional HtrA protease without requiring any specific transformation.

Rejection of the Claims Under 35 U.S.C. § 102(b)

Claims 11, 13, 14, 16, and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Vos *et al.*

Claims 11, 13, 14, and 16 as they stand are directed to a method of producing a desired protein comprising culturing a Gram positive bacterial strain of the *Streptococcaceae* family, wherein the bacterial strain has a genome of less than or equal to 3.2 Mb, and wherein the bacterial strain does not express a functional HtrA protease. Claim 17 is directed to a Gram positive bacterial strain of the *Streptococcaceae* family and having a genome of less than 3.2 Mb in size. The cited reference, Vos *et al.*, does not disclose the claimed method or claimed bacterial strain meeting the limitations recited in the claims.

The Office Action alleges that the protease which is rendered non-functional in the cited reference meet the limitations of the claims because the specification defines "HtrA protease" as "any serine protease of the trypsin type, having functional and structural similarities with the HtrA protease of *E. coli* which are sufficient for it to be included in the same family." However, Applicants respectfully submit that the definition for "HtrA protease" set forth on page 8, lines 6-20, also include the limitation that the protease must have functional and structural similarities with the HtrA protease of *E. coli* which are sufficient for it to be included in the same family, such as having a catalytic triad formed by the three amino acids His, Asp, and Ser of the consensus regions –GY--TN-**H**V-, **D**-AV----, and GNSGG-L-N-G--IGIN. The cited reference does not disclose a protease having these structural limitations.

The Office Action states that the cited reference teaches a method of producing a protein of interest, *i.e.* casein. Applicants respectfully submit that casein is not produced by the bacteria, because casein is present in the culture media. In fact, the cited reference does not teach

expression of a desired protein from a bacterial strain. The cited reference discloses a method of modifying the extracellular proteases in order to obtain mutant proteases that have a different specificity towards casein.

Accordingly, the cited reference does not teach the claimed invention, and therefore does not anticipate the claims.

Rejection of the Claims Under 35 U.S.C. § 103(a)

Claims 11, 13, 14, and 16 are rejected 35 U.S.C. § 103(a) as being unpatentable over Dougan *et al.* or Georgiou *et al.*, in view of Smeds *et al.*

Claims 11, 13, 14, and 16 as they stand are directed to a method of producing a desired protein comprising culturing a Gram positive bacterial strain of the *Streptococcaceae* family, wherein the bacterial strain has a genome of less than or equal to 3.2 Mb, and wherein the bacterial strain does not express a functional HtrA protease. Claim 17 is directed to a Gram positive bacterial strain of the *Streptococcaceae* family and having a genome of less than 3.2 Mb in size. Neither Dougan *et al.*, Georgiou *et al.*, nor Smeds *et al.* teach a Gram positive bacterial strain of the *Streptococcaceae* family that does not express a functional HtrA protease. In fact, the cited references do not disclose a Gram positive bacteria of the *Streptococcaceae* family.

As explained in the last Office Action, Dougan *et al.* teach a Gram negative bacterial strain having a mutation in the *degP* gene of the HtrA family for expressing a heterologous antigen. The *degQ* and *degS* genes of the HtrA family are still intact and functional. Thus, the *htrA* protease gene of this bacteria is still functional with respect to the *degQ* and *degS* genes. Likewise, Georgiou *et al.* disclose the use of mutant Gram negative bacteria that are multiply protease deficient for producing proteolytically sensitive polypeptides. Specifically, Georgiou *et al.* teach mutant Gram negative bacteria deficient in DegP, OmpT, and/or Protease III protease. The *degQ* and *degS* genes of the HtrA are intact, the *htrA* gene must be functional. In fact, Dougan *et al.* and Georgiou *et al.* teach that the degradation of exported protein occur in these bacteria which suggest that the bacteria express a functional HtrA protease. Moreover, the cited references teach away from the claimed invention because they teach that the inactivation of additional proteolytic enzymes will compromise the cell's viability. Accordingly, neither Dougan *et al.* nor Georgiou *et al.* teach the claimed invention.

Smeds *et al.* describe a strain of *Lactobacillus helveticus* which is not a member of the *Streptococcaceae* family. Smeds *et al.* do not teach expression of a desired protein using this strain of bacteria nor the export of the desired protein outside of the bacteria.

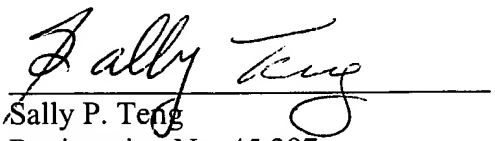
The cited references are not directed to an invention that is analogous to the claimed invention. There is no motivation to combine the references. Even if the references were combined, there is no reasonable expectation of success in arriving at the claimed invention. Thus, the cited references do not render the claimed invention obvious.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, they are invited to telephone the undersigned at their convenience.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which my be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **Constructive Petition for Extension of Time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted,
Morgan, Lewis & Bockius LLP



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